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3 SEP 1999

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03SEP99 E474101-1 D05022
P01/7700 0.00 - 9920772.2

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference

PA9947

2. Patent application number
(The Patent Office will fill in this part)

9920772.2 — 3 SEP 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NYCOMED AMERSHAM PLC
Amersham Laboratories
White Lion Road
Amersham
Bucks HP7 9LL. GB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

GB 7395288001

4. Title of the invention

IMPROVED CONTAINER COMPOSITION FOR RADIOPHARMACEUTICAL AGENTS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Dr Anthony John ROLLINS

Nycomed Amersham plc
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Bucks HP7 9LL. GB

Patents ADP number *(if you know it)*

5844139002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

NO

Improved Container Composition for Radiopharmaceutical Agents

Summary of the Invention

The present invention relates to improved containers for radiopharmaceutical agents, which are metal complexes, where the container has an internal coating of SiO_2 preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Field of the Invention

US 4385086 (1983) discloses the use of glass (and other materials) coated with highly oxidised silicon, to prevent the leaching of metal ions from the glass into the contents.

FR 2697014 A1 (1994) discloses the silica coating of the bottles, flasks, ampoules etc. for use with food or liquid pharmaceutical products to reduce leaching of metals into the liquid contents of the container.

DE 29609958 U1 discloses that glass containers having an internal coating of SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or diagnostic solutions.

JP 11-99192A discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as ^{201}Tl solution to the surface of the glass. No specific reference to radiopharmaceuticals which are metal complexes is made, and the main thrust of the invention is to a radiopharmaceutical vial having reversed text characters on the surface of the container. The silica coating of these vials is manufactured by the method described in JP 2815595 B which involves treating the glass surface with a silyl tetraisocyanate vapour in a carrier gas, followed by heating at high temperatures. JP 2815595 B also discloses that such a silica coating is useful to prevent leaching of impurities such as alkali from the glass into medical products.

Summary of the Invention

The present invention relates to silica-coated containers in combination with the following categories of products:

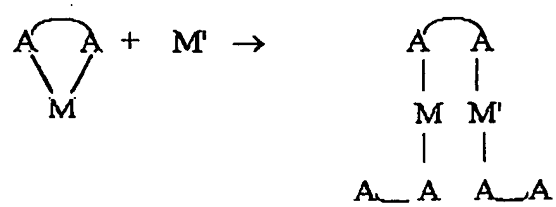
(i) radioactive radiopharmaceutical products which are metal complexes,
(ii) lyophilised kits for the preparation of radiopharmaceutical metal complexes, especially for the preparation of ^{99m}Tc radiopharmaceuticals.

from the glass, can have a significant effect on the radiochemical purity of the ML product, by increasing the levels of free radiometal (M) impurity. Such free radiometal could then generate further radioactive impurities by undergoing e.g. redox reactions.

In addition to, or instead of equation (i), complexation (ii) may also occur. This leads to the presence of undesirable M'L impurities in the product ML. M'L is non-radioactive, but for a radiopharmaceutical agent, the ligand (L) is usually present in vast chemical excess over the metal (M) present, hence if M' has any affinity for L, equation (ii) is always likely to occur.

When L is a multidentate ligand, such as a chelating agent the number of metal donor sites (A) per ligand (L) may be 2, 3, 4, 5, 6 or 8 typically. In that case, a process which is a special case of equation (i) above could occur as follows:

(iii)



where the free A donors can complex to further M/ M' atoms etc. <u>note</u>: the curved lines represent the chain of atoms linking the A groups.

leading to dimeric or oligomeric binuclear or polynuclear metal complexes involving both radiometal M and non-radioactive metal M'. The leached metal (M') may be less amenable to chelation by polydentate ligand (L), and hence favour such polynuclear species, even when M does not. This would result when the energetics are less favourable, e.g. M' is too small for two A groups to coordinate without undue steric interactions from either the A groups themselves, or the ligand backbone linking the A groups. Clearly, the greater the denticity of the ligand L (i.e. the greater the number of A metal donor sites), the greater the potential complexity of the product.

In the light of the above, it can be seen that the influence of leachable metal ions (M'), can have effects which go far beyond just metal ion impurities alone. This is important for metal complex radiopharmaceutical products and is not recognised by JP 11-99192A which relates only to adsorption effects *via* an ion exchange mechanism for uncomplexed i.e. free radiometal ions, e.g. ^{201}Tl as Tl^+ with the Na^+ and K^+ ions of the glass container walls.

For uncoated glass containers, the leaching of metal ions from the glass can be overcome by washing with dilute aqueous acid solutions (to remove relatively labile leachable metal ions), following by rinsing and (optionally) drying steps, before the container is charged with product. The layer of SiO_2 suppresses any such leaching of metal ions (M'), and hence obviates the need for any such steps. This is particularly important for diagnostic products intended for human use such as radiopharmaceuticals which are typically administered by injection into the human bloodstream, since these washing steps must be done in a sterile manner. Hence although such steps may be straightforward, their removal represents a significant improvement.

Experimental

Example 1

Groups of 10 Type I Plus vials (Schott Glas) were subjected to a series of stress tests to demonstrate the robustness of the silica coating with respect to leachable ions.

The basic test was the resistance of the coating to the leaching of cations when autoclaved with 0.04M aqueous HCl. This test was performed after vials were exposed to the following stress conditions:

1. Vials washed, pyrogen baked then 2ml of 0.04M HCl added and vials sealed. Test vials autoclaved then stored upright at 40°C before testing for leachable cations.
2. Vials stored for 6 weeks at -196°C, then washed and pyrogen baked. 2ml of 0.04M HCl added to each vial, vials then sealed, autoclaved and tested for leachable cations.
3. As test 2, except that the vials were stored at -70°C, -20°C, +20°C and +40°C/75% relative humidity.
4. Further tests included vials pyrogen baked 3 times, vials containing 0.04M HCl autoclaved three times, vials gamma irradiated (35.4 – 36.2 kGy dose).

All test solutions were measured by ICP for silicon, sodium, aluminium and boron, those cations considered to be most leachable from the vial surface. The results are given in Table 1.

Table 1

Test Number		Si	Na	Al	B
1		0.149	Nd	0.006	Nd
2		0.163	Nd	Nd	Nd
3	-70°C	0.167	Nd	0.00	0.00
	-20°C	0.193	0.005	0.002	0.002
	+20°C	0.193	0.009	0.005	0.003
	+40°C	0.236	0.006	0.002	0.002
4	bake	0.110	Nd	0.010	Nd
	X3	0.378	0.012	Nd	0.006
	Gamma	0.102	0.003	Nd	Nd

Note: each table entry is the mean of 12 batch runs, each batch of 10 vials (i.e. 120 vials tested), expressed in $\mu g/cm^3$ of test solution.

Nd = not detected. Detection limits (in $\mu g/cm^3$):

Si – 0.003
Na – 0.004
Al – 0.004
B – 0.004

All of the results were satisfactory, particularly for the key cations sodium and aluminium, each of which had mean values of approximately 0.01 μg per ml of test solution. These very low levels demonstrate the robustness of the silica coating under stress conditions.

Example 3: Oxine Ligand Loss

20 P6 glass vials were rinsed with water, drained and baked to depyrogenate. Each vial was then dispensed with a solution containing 50 μg of oxine, and the oxine content determined by HPLC at various time points. The results are shown in Table 2:

Table 2: Oxine Loss by HPLC

Time Point	Oxine in Solution	Solution/ Suspension Al(ox)3	Glass oxine	Glass Al(ox)3	Recovery (%)
initial	25.2	8.5	5.1	2.3	82
reference	20.1	26.7	3.1	6.0	~100
expiry	20.3	27.7	2.5	7.3	~100
expiry +14 days	19.0	16.4	6.6	5.7	95

HPLC System
Column: Hamilton PRP1, 150 x 4.1mm, μm particle size
Eluent A: 25 mM KH_2PO_4 adjusted to pH 10.3 – 10.5 with KOH
Eluent B: Acetonitrile
Gradient: $0\%\ B \xrightarrow{15\ min} 50\%\ B \xrightarrow{5\ min} 50\%\ B \xrightarrow{3\ min} 0\%\ B$
Flow Rate: 1.75ml/min.
Injection volume: 20μg
Detection: UV at 254nm, path length 10mm
System control and data processing: Gilson 715 System Controller

The system was calibrated using 50 μg/ml solutions of oxine in water and aluminium oxinate in acetonitrile. Retention time of oxine ca. 15 – 15.2 min. Al(oxinate) ca. 17 min.

For solution/suspension measurements, samples of vial contents were taken directly and injected. The oxine and aluminium oxinate peaks were each integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. The results were then scaled to give a total solution/suspension content. For measurements of oxine and aluminium oxinate adsorbed on the vial walls, the vial was decapped, drained and carefully rinsed with 0.2ml acetonitrile. 20 μg of the rinse solution was injected, the peaks integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. Previous experiments had shown oxine losses to the vial stopper to be negligible.

Example 4
Freeze-dried kits using USP Type 1 glass vials (i.e. P6 uncoated vials) containing the following formulation were prepared:

meso – DMSA	1.0mg
$SnCl_2 \cdot 2H_2O$	0.42mg
ascorbic acid	0.7mg
inositol	50.0mg